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**In re PCT International
Application No.:**

PCT/CA2005/000472

Filed: **March 30, 2005**

Applicant: **Canadian Blood Services et al.**

Title: **METHOD FOR TREATING AUTOIMMUNE
DISEASES WITH ANTIBODIES**

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VIA FACSIMILE

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Sir:

SUPPLEMENTARY RESPONSE UNDER ARTICLE 34 PCT

In response to the Written Opinion mailed July 27, 2005 and the International Examiner's telephone communication with the Applicant's correspondent on June 19, 2006, please amend the application as follows:

IN THE DESCRIPTION

Please replace page 7 of the description originally filed with amended description page 7 attached hereto.

IN THE CLAIMS

Please replace claim pages 32 to 38 filed with the amendment/response under Article 34 PCT on January 30, 2006 with amended pages 32 to 39 attached hereto.

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REMARKS

The Applicant submits herewith additional amendments and comments pursuant to the Examiner's telephone communication of June 19, 2006 in order to place the application in a more favourable condition for further examination.

Each of the independent claims, i.e. present claims 1, 18, 33 and 48, have been amended to specify "an immune thrombocytopenia or inflammatory arthritis", as supported throughout the claims and description, for instance on description page 2, lines 17 to 26.

The "antibody" recited in these claims is further defined as an "IgG" antibody, as supported throughout the description, for instance on description page 6, line 29.

It is further specified in amended claims 1, 18, 33 and 48 that the claimed "methods of treatment", "composition" and "use" involve the administration of an IgG antibody "and/or a complementary soluble antigen thereof". This amendment is supported throughout the originally filed application, for instance, on description page 3, lines 18 to 23.

The phrase "by means of an in vivo antibody-antigen interaction, without invoking the biological function of the antigen" has been added in amended claims 1, 18, 33 and 48. This amendment is inherently supported throughout the original description and claims, for instance on description page 4, lines 15 to 27. In this respect, since it is shown in the present application that the therapeutic effect is dependent upon the host animal expressing an Fc receptor (Fc_γRIIB), and since Fc receptors are not known to interact with antigens but only antibodies, it is apparent that it is the antibody portion of the conjugate that determines function and not any special attributes of the antigen. Thus, the antibody-antigen interaction does not invoke the biological function of the antigen.

Amended claims 1, 18, 33 and 48 are further defined by the phrase "results in selective binding of said antibody with said soluble antigen in vivo in said mammal". This amendment is supported throughout the description, for instance on original description page 4, lines 17 to 21.

New dependent claims 6, 25, 39 and 55 have been added to claim an embodiment whereby the IgG is pre-existing, and in that case that it is the soluble antigen that is administered. This is supported by the description on page 3, lines 18 to 23.

New dependent claims 9, 29, 42 and 59 have been added to claim the embodiment whereby the antigen is endogenous, and antibody is administered.

The Applicant has also taken this opportunity to effect more minor revisions throughout the claims, without, however, adding any new subject matter.

In addition, a clerical error made on original description page 7, lines 10 to 12 has been rectified in the replacement description page submitted herewith. The sentence in question now correctly reads "It was found that OVA-RBC + anti-OVA ameliorated immune thrombocytopenia in normal mice and Fc γ IIB $^{-/-}$ mice, while soluble OVA + anti-OVA was ineffective in Fc γ RIIB $^{-/-}$ mice". Support for the correction made to this sentence is obtained from original description page 18, lines 7 to 29.

No new subject matter is added by virtue of the above-described amendments.

The Applicant additionally wishes to clarify for the Examiner that the three antigens for which testing results are provided in the specification are non-limiting examples of the antigens that may be used in accordance with the present invention. It is the formation of an antibody-antigen conjugate in vivo that is required to provide the desired therapeutic effect. This effect has been achieved with four different IgG preparations (polyclonal anti-OVA, monoclonal anti-OVA, polyclonal anti-mouse albumin and polyclonal anti-transferrin) but not with the control monoclonal and control polyclonal IgG preparations. Since the therapeutic effect has been demonstrated with all three of the antigens tested, one skilled in the art would recognize that the function of the antigen is not a factor in the effect, other than serving as something which binds to the IgG antibody. In addition, it is shown in the application that the antibody-antigen conjugate works when the conjugate is injected into a mouse directly, as well as when it is incubated in vitro in the presence of splenic leukocytes for 30 minutes followed by washing of the leukocytes and injecting the washed leukocytes into a mouse with thrombocytopenia (Fig. 12). Thus the antibody-antigen conjugate binds the leukocytes, which is key in the amelioration of the immune thrombocytopenia. The antibody-antigen conjugate binds to activating Fc γ receptors. Further, the antibody-antigen conjugate function in vivo is dependent upon Fc receptors (Fig. 13) and thus it is the antibody (which binds Fc receptors) that delivers the signal. Thus, the choice of antigen is unimportant other than being able to bind an antibody.

The present inventors have specifically attempted to test the concept that an in vivo antibody-antigen conjugate recapitulates the therapeutic (immunological) effects of IVIg administration in the amelioration of immune thrombocytopenia (IT). In particular, a model antigen which does not exist in the host nor has any known (immunologically relevant) function was selected, i.e. ovalbumin. The work demonstrates that only when ovalbumin is injected under conditions where it will form a conjugate with a complementary IgG antibody, is there a resolution of the immune thrombocytopenia (an increase in the platelet count). The ovalbumin alone as well as the complementary Ab alone have no effect. Also, the injection

of the ovalbumin plus a non-complementary IgG antibody does not increase the platelet count. To substantiate that it is the formation of a conjugate between an IgG antibody and its corresponding antigen, the inventors employed three IgG preparations, one specific to endogenous mouse albumin, one specific to mouse transferrin and one without any known specificity (control IgG).

It is thus submitted that the presently amended claims are supported by the teachings of the description and in compliance with Article 6 of the PCT.

It is further submitted that none of the cited references D1 to D5 teach or imply a "method of treatment", "composition" or "use" of the presently amended claims, and it is therefore asserted that the claims define novel and inventive subject matter in accordance with Article 33(2) and Article 33(3) of the PCT.

In view of the preceding comments and amendments, the Applicant believes the present application is in a condition meriting a positive and favourable International Preliminary Report on Patentability.

Respectfully,

Ogilvy Renault LLP/S.E.N.C.R.L., s.r.l.



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thrombocytopenia. Mice injected with soluble ovalbumin (OVA) or OVA conjugated to RBCs (OVA-RBC) in the presence of anti-OVA, were both significantly protected from immune thrombocytopenia.

5 Both of these therapeutic regimes functioned independent of complement activity and both regimes also blocked reticuloendothelial function as assessed by clearance rates of fluorescent sensitized syngeneic RBCs. Soluble OVA or anti-OVA alone did not have any direct effect on immune
10 thrombocytopenia in mice. It was found that OVA-RBC + anti-OVA ameliorated immune thrombocytopenia in normal mice and Fc γ RIIB^{-/-} mice, while soluble OVA + anti-OVA was ineffective in Fc γ RIIB^{-/-} mice. In addition, IgG specific for murine albumin and specific for transferrin also effectively
15 inhibited ITP. Thus, IgG antibodies directed to soluble antigens can inhibit or reverse immune thrombocytopenia in an Fc γ RIIB-dependent manner, whereas antibodies directed to a cell-associated antigen function independent of Fc γ RIIB expression.

20 Materials and Methods:

Reagents:

The monoclonal antibody specific for integrin α _{IIb} β ₃ (rat IgG₁, clone MWReg 30) was purchased from BD Pharmigen (Mississauga, ON, Canada). Monoclonal murine anti-OVA (IgG₁, clone OVA-14), rabbit polyclonal anti-OVA, 1-ethyl-3-(3-dimethylamino-propyl) carbodiimide (EDAC), OVA (grade V), and PKH26 red fluorescent cell linker kit were purchased from Sigma (Oakville, ON, Canada). IVIG was Gammimune, 10% from Bayer (Elkhart, IN). Cobra Venom Factor (CVF), FITC-conjugated 30 F(ab')₂ anti-rabbit IgG, and control rabbit IgG, were purchased from Cedarlane Laboratories Ltd (Hornby, ON, Canada). Rabbit anti-mouse albumin (IgG fraction), and rabbit anti-mouse transferrin (IgG fraction), were purchased from Research

AMENDED SHEET

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